Comments on:

ENVIRONMENTAL TOBACCO SMOKE:

A GUIDE TO WORKPLACE SMOKING POLICIES

[Draft] EPA 400/6-90/004

Response Addressing:

Chapter 3: Health Effects of ETS

Section: Cancer at Other Sites

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SUMMARY: The authors of the EPA's draft document, "Environmental Tobacco Smoke: A Guide to Workplace Smoking Policies" (The "Guide") state, in Chapter 3, page 18, that smoking is related to brain tumors, nasal sinus cancer, genital, breast, endocrine and cervical cancers in adults and brain tumors in infants whose mothers were exposed to ETS while pregnant. Reference to the alleged relationship between smoking or ETS and those cancers is inappropriate because epidemiologic studies cannot demonstrate a causal relationship and deficiencies in the studies call into question the authors' conclusions that ETS may even be associated with these diseases. The Guide should limit its conclusions to the point: "At this point the data are too limited to be conclusive." [The Guide, p. 18].

COMMENTARY: The section "Cancer At Other Sites," referenced six published reports on studies of the relationship between ETS and cancer other than the lung. The studies can be divided into four categories:

1. The 1989 study by Slattery, *et al.* [1] which reported an association between cervical cancer and ETS.

2. The 1982 study by Preston-Martin, *et al.* [2] which reported an association between ETS and childhood brain tumors.

3. The 1984 study by Hirayama [3] which reported that women exposed to spousal ETS are at elevated risk for nasal sinus cancer, brain tumors, breast cancer, and cancer of all sites.

4. Three studies by Sandler, *et al.* [4-6] which reported associations between several cancer types and exposure to ETS.

Comments concerning these four categories of studies are given below:

Analysis of Category 1- The Slattery Study [1]

Zhang, Wynder, and Harris (American Health Foundation, Valhalla, New York), have critiqued the Slattery study in a letter to the editor of JAMA [7]. They concluded that "the classification of passive smoke exposure as a risk factor for cervical cancer seems premature."

Analysis of Category 2- The Preston-Martin Study [2]

This study has at least four major deficiencies:

1. Preston Martin, *et al.* report an increased risk (OR, 1.5; $p = 0.03$) for childhood brain tumors associated with the mother's living with a smoker during pregnancy. However, they found no association between maternal smoking during pregnancy and childhood brain tumors. Since cigarette smokers are exposed to both mainstream smoke and to much higher levels of ETS than are nonsmokers, cigarette smokers and

their children would be expected to be at an increased risk of brain tumors if the authors' hypothesis were correct.

2. Exposure to several common substances (other than ETS) during pregnancy was also reported to be associated with childhood brain tumors. Exposure to antihistamines (OR, 3.4; p= 0.002), face makeup (OR, 1.6; p = 0.02), diuretics (OR, 2.0; p = 0.03), incense (OR, 3.3; p = 0.005), and cured meat, all were associated with increased risk. The variety of different substances reported to be associated with childhood brain tumors in this study suggests that these results are likely to be due to confounding.

3. Exposure estimates used in the calculations were determined by interview and questionnaire data. Slight inaccuracies in exposure estimates could affect the significance of the relative risk estimates reported in the study.

4. Nine different histological types of brain tumors were combined in a statistical meta-analysis of the data. Meta-analysis must be used with great care. In this study, the authors assume that the different tumors are caused by the same agents. If this (bold) assumption is incorrect, then the "robustness" of any potential correlation is suspect.

Analysis of Category 3 - The 1984 Hirayama Study [3]

In his study, Hirayama reported an increased risk in nonsmoking wives with smoking husbands for nasal sinus cancer, brain tumors, and possibly breast cancer. The reported increase in risk for the spouses of the smokers may be the result of "data dredging". "Data dredging" refers to the process of examining a large number of potential associations by a number of different methods until several associations that fit the hypothesis in question are dredged up by chance [8].

Hirayama examined a large number of associations and found some of them to be positive (lung, brain, sinus, and possibly breast). He also reported that "[n]o significant association was observed with other cancers such as those of the mouth, pharynx, esophagus, stomach, colon, rectum, liver, pancreas, peritoneum, cervix, ovary, urinary bladder, skin, bone, malignant lymphoma, or leukemia, the direction of this trend being evenly distributed to both the plus-side (risk increases with the extent of husband's smoking habit) and the minus-side (risk decreases with the extent of husband's smoking habit)".

Hirayama's results are inconsistent with the results from epidemiology studies conducted on cigarette smokers. Cigarette smokers are exposed to much higher levels of ETS than are ETS-exposed nonsmokers. The hypothesis that exposure to ETS increases the risk of cancer predicts that cancers that are not associated with cigarette smoking should not be associated with ETS exposure. This is not what Hirayama reports. Brain cancer and breast cancer are not associated with cigarette smoking [9,10]. Hirayama finds positive associations between ETS exposure and these non-smoking-associated tumors. Hirayama

found no association between exposure to ETS and a variety of cancers that have been epidemiologically associated with cigarette smoking, including cancer of the esophagus, pancreas, cervix, and urinary bladder [9]. Therefore, Hirayama has not demonstrated an association between ETS and cancer that is consistent with reported epidemiological data in the literature.

Analysis of Category 4 - The Sandler Studies [4-6]

There are several significant lifestyle differences between smokers and nonsmokers. Smokers consume a diet significantly higher in saturated fat and lower in fruits and vegetables than nonsmokers [11-13]. Smokers exercise significantly less than nonsmokers [14]. They also sleep less and consume more alcohol than nonsmokers [15]. Each of these factors is associated with chronic diseases such as cancer and would tend to increase the smokers' relative risk of developing such diseases.

Also, significant differences in lifestyle exist between the spouses of smokers and the spouses of nonsmokers. Perusse, *et al.* [16] demonstrated familial aggregation in physical fitness, coronary heart disease risk factors, and pulmonary function measurements. Other investigators have reported significant dietary differences between the families of smokers and the families of nonsmokers. Sidney, *et al.* [17] reported that the self-reported mean dietary intake of carotene is lower in nonsmokers exposed to ETS at home than in nonsmokers not exposed to ETS at home. Many studies have reported that a low intake or blood level of carotene is a risk factor for cancer, Ziegler, [18]. Sidney, *et al.* [17] also found

a higher proportion of current alcohol consumers and a slightly higher mean body mass index in the exposed subgroup despite its considerably lower mean age.

The studies by Sandler, *et al.* [4-6] do not take into account all of the relevant lifestyle factors that could affect relative risk ratios. One Sandler, *et al.*, study [4] provides several good examples of the failure to adjust for confounding variables. In this study, the authors report "statistically significant risks in relationship to passive smoking are seen for breast cancer, cervical cancer, and endocrine cancers". They reported a two-fold risk of breast cancer in ETS exposed women after adjustment for education, race, age, smoking status, and parental smoking. However, Sandler, *et al.* [4] did not adjust for the four most important breast cancer risk factors other than age: Diagnosis of premenopausal breast cancer in a mother or sister, previous history of proliferative benign breast disease, age at first parity, and diet [19]. Sandler , *et al.* [4] also reported a two-fold risk for cervical cancer associated with ETS exposure after adjustment for age, race, smoking status, and smoking by parents. In this case again, Sandler, *et al.* [4] did not adjust for the most important cervical cancer risk factor: Sexual history of both spouses. Layde and Broste [20] discussed the importance of controlling for this factor in smoking and cervical cancer studies in their 1989 review:

> "In their [sic] summary (IARC's) of the association of cigarette smoking and cervical cancer, the working group stated "for cervical cancer, it is reasonable to suppose that there is a specific causal agent - most probably an infective agent transmitted sexually. Since this agent has not been unequivocally identified, and, in particular, was not included in the studies under review, surrogate measures have been included

to reflect the degree of sexual activity. Smoking is positively related to sexual activity. Any observed crude association between smoking and risk of cervical cancer may be confounded. Since the specific factor by which the analysis should be adjusted is not known, the confounding effect can be removed only partially."

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